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(71) Applicant *(for all designated States except US)*: BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH [DE/DE]; Carl-Giesecke-Strasse 3, D-37079 Göttingen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BRYSCH, Wolfgang [DE/DE]; Am Goldgraben 20, D-37073 Göttingen (DE). SCHLINGENSIEPEN, Karl-Hermann [DE/DE]; Bovender Strasse 5, D-37120 Bovenden (DE). SCHLINGENSIEPEN, Reimar [DE/DE]; Am Goldgraben 13, D-37073 Göttingen (DE). SCHLINGENSIEPEN, Georg-F. [DE/DE]; Am Goldgraben 20, D-37073 Göttingen (DE).

(74) Agents: MEYERS, Hans-Wilhelm et al.; Deichmannhaus am Hauptbahnhof, D-50667 Köln (DE).

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(54) Title: ANTISENSE NUCLEIC ACIDS FOR THE PREVENTION AND TREATMENT OF DISORDERS IN WHICH EXPRESSION OF c-erbB PLAYS A ROLE

(57) Abstract

The present invention is related to an antisense-nucleic acid or effective derivatives thereof hybridizing with an area of the messenger RNA (mRNA) or the DNA, encoding the $p185^{erbB-2}$ receptor (also termed c-erbB-2, HER2 or neu), a pharmaceutical composition, comprising an antisense nucleic acid or effective derivatives thereof hybridizing with an area of the messenger RNA (mRNA) or the DNA, encoding the c-erbB-2 receptor as well as the use of said antisense nucleic acids and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis.

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Antisense nucleic Acids for the prevention and treatment of disorders in which expression of c-erbB plays a role

The present invention is related to an antisense-nucleic acid or effective derivatives thereof hybridizing with an area of the messenger RNA (mRNA) or the DNA, encoding the $p185^{erbB-2}$ receptor (also termed c-erbB-2, HER2 or neu), a pharmaceutical composition, comprising an antisense nucleic acid or effective derivatives thereof hybridizing with an area of the messenger RNA (mRNA) or the DNA, encoding the c-erbB-2 receptor as well as the use of said antisense nucleic acids and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis.

ErbB-2 is a putative growth factor receptor with an intracellular tyrosine kinase activity that is amplified and/or overexpressed by tumor cells in a variety of neoplasms including breast cancer, lung cancer, esophageal and gastric cancer, bile duct carcinoma, bladder cancer and ovarian cancer.

In breast carcinoma patients, an amplification and overexpression of the c-erbB-2 gene in the tumor tissue has been shown to correlate with a poor clinical prognosis. Overexpes-

sion of $p185^{erbB-2}$ in non-small-cell lung carcinoma has been shown to impart resistance to a number of chemotherapeutic agents.

WO 93/09788 discloses a method for inhibiting the proliferation of cells which contain an erb B2/neu gene site. The method involves administering a therapeutic dose of an oligonucleotide which is capable of forming a colinear triplex with the promoter region of the erb B2/neu gene.

WO 92/19732 discloses sense and antisense oligonucleotides, namely closed oligonucleotides. These compounds may be used pharmacologically as sense or antisense molecules. It is generally described the therapeutic use of oligonucleotides as sense or antisense agents.

WO 92/13063 discloses a method for effecting expression of growth factors and growth factor receptors in cells or in multicellular animals and methods for testing compounds as effectors of transcription of growth factors and growth factor receptors.

The article "Chemically Modified Oligodeoxynucleotide Analogs as Regulators of Viral and Cellular Gene Expression" in Gene Regulation: Biology of Antisense RNA and DNA discloses in general the use of chemically modified oligonucleotides in the antisense technology.

It is an object of the present invention to provide a compound for the treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis.

The c-erbB-2 antisense-oligonucleotide of the invention solving the problem addressed above have the sequences as disclosed in the sequence listing under Seq. ID No. 1-105, having a DNA- or RNA-type structure. The control oligonucleotide has the sequence as disclosed in the sequence

listing under Seq. ID No 106, having a DNA- or RNA-type structure.

The antisense nucleic acids of the invention, were able to strongly inhibit the expression of the $p185^{erbB-2}$ protein, tyrosine kinase activity and cell growth in a variety of tumor cells including breast cancer cells. Untransformed normal fibroblasts were not growth inhibited by the anti-c-erbB-2 antisense compounds. This suggests that $p185^{erbB-2}$ plays a pathogenetic role in the growth of the above mentioned tumor cells.

Furthermore, surprisingly, the immune response to a variety of neoplasms was significantly increased by the use of the antisense nucleic acids of the invention. Immune cell growth and activity was stimulated in co-culture assays culturing tumor cells and peripheral blood monocytes together.

Surprisingly, the antisense nucleic acids of the invention, also acted as strong inhibitors of angiogenesis. This suggests, that either the secreted truncated form of the c-erbB-2 protein or the full receptor protein may play a causal role in pathological neoangiogenesis.

According to the invention antisense nucleic acids or effective derivatives thereof which hybridize with an area of the mRNA or DNA coding for $p185^{erbB-2}$ can effectively treat the diseases addressed above. The antisense nucleic acid is able to hybridize with regions of $p185^{erbB-2}$ mRNA. It is understood by the skilled person that fragments of the antisense nucleic acids and antisense nucleic acids containing these sequences work according to the invention so long as production of $p185^{erbB-2}$ is reduced or inhibited.

According to the invention the antisense-oligonucleotides are obtainable by solid phase synthesis using phosphite triester chemistry by growing the nucleotide chain in 3'-5'

direction in that the respective nucleotide is coupled to the first nucleotide which is covalently attached to the solid phase comprising the steps of

- cleaving 5'DMT protecting group of the previous nucleotide,
- adding the respective nucleotide for chain propagation,
- modifying the phosphite group subsequently cap unreacted 5'-hydroxyl groups and
- cleaving the oligonucleotide from the solid support,
- followed by working up the synthesis product.

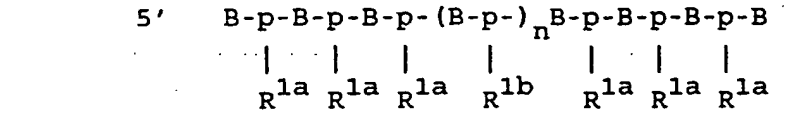
The chemical structures of oligodeoxy-ribonucleotides are given in figure 1 as well as the respective structures of antisense oligo-ribonucleotides are given in figure 2. The oligonucleotide chain is to be understood as a detail out of a longer nucleotide chain.

In figure 1, lit. B means an organic base such as adenine (A), guanine (G), cytosine (C) and thymine (T) which are coupled via N9(A,G) or N1(D,T) to the desoxyribose. The sequence of the bases is the reverse complement of the genetic target sequence (mRNA-sequence). The modifications used are

1. Oligodeoxy-ribonucleotides where all R^1 are substituted by

1.1 $R^1 = O$
1.2 $R^1 = S$
1.3 $R^1 = F$
1.4 $R^1 = CH_3$
1.5 $R^1 = OEt$

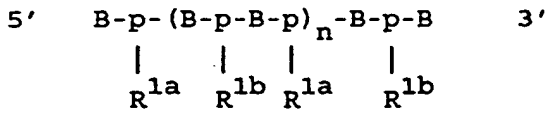
2. Oligodeoxy-ribonucleotides where R^1 is varied at the internucleotide phosphates within one oligonucleotide



where B = deoxy-ribonucleotide dA, dC, dG or dT depending on gene sequence
p = internucleotide phosphate
n = an oligodeoxy-ribonucleotide stretch of length 6 - 20 bases

2.1	R^{1a} = S;	R^{1b} = O
2.2	R^{1a} = CH_3;	R^{1b} = O
2.3	R^{1a} = S;	R^{1b} = CH_3
2.4	R^{1a} = CH_3;	R^{1b} = S

3. Oligodeoxy-ribonucleotides where R^1 is alternated at the internucleotide phosphates within one oligonucleotide



where B = deoxy-ribonucleotide dA, dC, dG or dT depending on gene sequence
p = internucleotide phosphate
n = an oligodeoxy-ribodinucleotide stretch of length 4 - 12 dinucleotides

3.2	R^{1a} = S;	R^{1b} = O
3.2	R^{1a} = CH_3;	R^{1b} = O
3.3	R^{1a} = S;	R^{1b} = CH_3

4. Any of the compounds 1.1 - 1.5; 2.1 - 2.4; 3.1 - 3.3 coupled at R^2 with the following compounds which are covalently coupled to increased cellular uptake

4.1 cholesterol
4.2 poly(L)lysine
4.3 transferrin

5. Any of the compounds 1.1 - 1.5; 2.1 - 2.4; 3.1 - 3.3 coupled at R^3 with the following compounds which are covalently coupled to increase cellular uptake

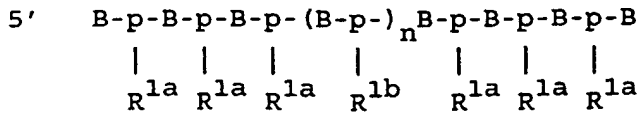
5.1 cholesterol
5.2 poly(L)lysine
5.3 transferrin

In the case of the RNA-oligonucleotides (figure 2) are the basis (adenine (A), guanine (G), cytosine (C), uracil (U)) coupled via N9 (A,G) or N1 (C,U) to the ribose. The sequence of the basis is the reverse complement of the genetic target sequence (mRNA-sequence). The modifications in the oligonucleotide sequence used are as follows

6. Oligo-ribonucleotides where all R^1 are substituted by

6.1 $R^1 = O$
6.2 $R^1 = S$
6.3 $R^1 = F$
6.4 $R^1 = CH_3$
6.5 $R^1 = OEt$

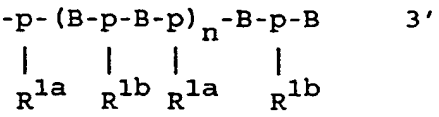
7. Oligo-ribonucleotides where R^1 is varied at the internucleotide phosphates within one oligonucleotide



where B = ribonucleotide A, C, G or T depending on gene sequence
p = internucleotide phosphate
n = an oligo-ribonucleotide stretch of length 4 - 20 bases

7.1 R^{1a} = S; R^{1b} = O
7.2 R^{1a} = CH_3; R^{1b} = O
7.3 R^{1a} = S; R^{1b} = CH_3
7.4 R^{1a} = CH_3; R^{1b} = S

8. Oligo-ribonucleotides where R^1 is alternated at the internucleotide phosphates within one oligonucleotide



where B = ribonucleotide A, C, G or T depending on gene sequence
p = internucleotide phosphate
n = an oligo-ribodinucleotide stretch of length 4 -12 dinucleotides

8.2 R^{1a} = S; R^{1b} = O
8.2 R^{1a} = CH_3; R^{1b} = O
8.3 R^{1a} = S; R^{1b} = CH_3

9. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3 coupled at R^2 with the following compounds which are covalently coupled to increase cellular uptake

9.1 cholesterol
9.2 poly(L)lysine
9.3 transferrin

10. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3

coupled at R3 the following compounds are covalently coupled to increased cellular uptake

10.1 cholesterol
10.2 poly(L)lysine
10.3 transferrin

11. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3; 9.1 - 9.3; 10.1 - 10.3 where all R^4 are substituted by

11.1 $R^4 = O$
11.2 $R^4 = F$
11.3 $R^4 = CH_3$

In a preferred embodiment of the oligonucleotides of the invention they are phosphorothioate derivatives, having a DNA- or RNA-type structure.

It is possible that one single individual sequence as mentioned above works as an antisense nucleic acid or oligonucleotide structure according to the invention. However, it is also possible that one strand of nucleotides comprises more than one of the sequences as mentioned above directly covalently linked or with other nucleotides covalently linked in between. Preferably, individual oligonucleotides are addressed.

In a preferred embodiment of these oligo-nucleotides they are phosphorothioate derivatives.

Modifications of the antisense-oligonucleotides are advantageous since they are not as fast destroyed by endogenous factors when applied as this is valid for naturally occurring nucleotide sequences. However, it is understood by the skilled person that also naturally occurring nucleotides having the disclosed sequence can be used according to

the invention. In a very preferred embodiment the modification is a phosphorothioate modification.

The synthesis of the oligodeoxy-nucleotide of the invention is described as an example in a greater detail as follows.

Oligodeoxy-nucleotides were synthesized by stepwise 5'-addition of protected nucleosides using phosphite triester chemistry. The nucleotide A was introduced as 5'dimethoxytrityl-deoxyadenosine(N-benzoyl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite (0.1 M); C was introduced by a 5'-dimethoxytrityl-deoxycytidine(N^4-benzoyl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite; G was introduced as 5'-dimethoxytrityl-deoxyguanosine(N^8-isobutyryl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite and the T was introduced as 5'-dimethodytrityl-deoxythymidine-N,N'-diisopropyl-2-cyanoethyl phosphoramidite. The nucleosides were preferably applied in 0.1 M concentration dissolved in acetonitrile.

Synthesis was performed on controlled pore glass particles of approximately 150 µm diameter (pore diameter 500 Å) to which the most 3' nucleoside is covalently attached via a long-chain alkylamine linker (average loading 30 µmol/g solid support).

The solid support was loaded into a cylindrical synthesis column, capped on both ends with filters which permit adequate flow of reagents but hold back the solid synthesis support. Reagents were delivered and withdrawn from the synthesis column using positive pressure of inert gas. The nucleotides were added to the growing oligonucleotide chain in 3'-> 5' direction. Each nucleotide was coupled using one round of the following synthesis cycle:

Cleave 5'DMT (dimethoxytrityl) protecting group of the previous nucleotide with 3-chloroacetic acid in dichloromethane followed by washing the column with anhydrous acetonitrile.

Then simultaneously one of the bases in form of their protected derivative depending on the sequence was added plus tetrazole in acetonitrile. After reaction the reaction mixture has been withdrawn and the phosphite was oxidized with a mixture of sulfur (S_8) in carbon disulfide/pyridine/-triethylamine. After the oxidation reaction the mixture was withdrawn and the column was washed with acetonitrile. The unreacted 5'-hydroxyl groups were capped with simultaneous addition of 1-methylimidazole and acetic anhydride/lutidine-/tetrahydrofuran. Thereafter, the synthesis column was washed with acetonitrile and the next cycle was started.

The work up procedure and purification of the synthesis products occurred as follows.

After the addition of the last nucleotide the deoxynucleotides were cleaved from the solid support by incubation in ammonia solution. Exocyclic base protecting groups were removed by further incubation in ammonia. Then the ammonia was evaporated under vacuum. Full-length synthesis products still bearing the 5'DMT protecting group were separated from shorter failure contaminants using reverse phase high performance liquid chromatography on silica C_{18} stationary phase. Eluents from the product peak were collected, dried under vacuum and the 5'-DMT protecting group cleaved by incubation in acetic acid which was evaporated thereafter under vacuum. The synthesis products were solubilized in the deionized water and extracted three times with diethylether. Then the products were dried in vacuo. Another HPLC-AX chromatography was performed and the eluents from the product peak were dialyzed against excess of Trisbuffer as well as a second dialysis against deionized water. The final products were lyophilized and stored dry.

The antisense-nucleic acid of the invention can be used as pharmaceutical composition or medicament. This medicament can be used for treating neoplasms and/or immune diseases

and/or diseases involving pathological angiogenesis in which the expression of c-erbB-2 derived receptor protein or truncated $p185^{c\text{-}erbB2}$ is of relevance for the pathogenicity. It can be used to reduce neoplastic cell growth in cells expressing $p185^{c\text{-}erbB2}$, to reverse resistance of tumor cells to the immune-response, to inhibit pathological angiogenesis and to stimulate the immune system.

The antisense nucleic acids of the invention are intermediate products of the pharmaceutical composition or medicament of the invention. The pharmaceutical composition may comprise besides the effective compound(s) suitable carrier agents, solvents and other ingredients known in the art for producing medicaments. Preferably, these agents facilitate the administration of the pharmaceutical composition of the invention. Typically, the pharmaceutical composition is administered as i.v. infusion or i.v. bolus injection. The amount of the active ingredient to be administered is typically in the range of 0.2 - 50 mg of the oligonucleotide per kg body weight per day, in particular 1 - 12 mg/kg body weight per day.

In principal the compound which can be used as an active compound in the pharmaceutical composition can be used as a diagnostic tool for evaluating whether the respective genes are expresses. Typically, radio active labelled nucleotides are hybridized by the method of northern blotting which is well-known in the art or in situ with a sample to be examined. The degree of hybridization is a measure for the degree of expression of the respective genes.

The effect of c-erbB2 specific antisense-oligonucleotides on neoplastic cell growth was investigated. It was demonstrated that antisense oligodeoxynucleotides as well as phosphorothioate modified nucleic acids, complementary to c-erbB2 mRNA could specifically inhibit $p185^{c\text{-}erbB2}$ protein expression and could to a significant amount reduce cell

proliferation in breast cancer cells, ovarian carcinoma cells and bladder cancer cells. Also, it could be shown that protein synthesis and S6 kinase activity were strongly reduced in tumor cells, treated with the antisense nucleic acid.

Furthermore, the immune response to a variety of neoplasms was significantly increased by the use of the antisense nucleic acids described below. Lymphocyte growth and activity was stimulated in co-culture assays culturing tumor cells and peripheral blood monocytes together.

Furthermore, the antisense nucleic acids described above, also acted as inhibitors of angiogenesis.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Biognostik Gesellschaft fuer biomolekulare Diagnostik mbH
(B) STREET: Carl-Giesecke-Str. 3
(C) CITY: Goettingen
(E) COUNTRY: Germany
(F) POSTAL CODE (ZIP): 37079

(ii) TITLE OF INVENTION: Antisense nucleic Acids for the prevention and treatment of disorders in which expression of c-erbB plays a role

(iii) NUMBER OF SEQUENCES: 106

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disc
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(v) CURRENT APPLICATION DATA:
APPLICATION NUMBER: EP 93120710.4

(2) INFORMATION FOR SEQUENCE ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

TTCATGTCTG TGCC 14

(2) INFORMATION FOR SEQUENCE ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

GTAGGTGAGT TCCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GTTGTGAGCG ATGA 14

(2) INFORMATION FOR SEQUENCE ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

CATAGTTGTC CTCAAAGA 18

(2) INFORMATION FOR SEQUENCE ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GGCATAGTTG TCCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

CATTGTCTAG CACG 14

(2) INFORMATION FOR SEQUENCE ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

CTCCATTGTC TAGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GTATTGTTCA GCGG 14

(2) INFORMATION FOR SEQUENCE ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

TCAAGATCTC TGTGAG 16

(2) INFORMATION FOR SEQUENCE ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CACAAAATCG TGTCCT 16

(2) INFORMATION FOR SEQUENCE ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

TCCTTCCACA AAATCG 16

(2) INFORMATION FOR SEQUENCE ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GTGGAAGATG TCCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TCTTGTGGAA GATGTC 16

(2) INFORMATION FOR SEQUENCE ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

TCTATCAGTG TGAGAG 16

(2) INFORMATION FOR SEQUENCE ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GGTTGGTGTC TATC 14

(2) INFORMATION FOR SEQUENCE ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

ACATCGGAGA ACAG 14

(2) INFORMATION FOR SEQUENCE ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

CCTTACACAT CGGA 14

(2) INFORMATION FOR SEQUENCE ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

ACAATCCTCA GAACTC 16

(2) INFORMATION FOR SEQUENCE ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

GCTCTGACAA TCCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

TGGTTGAAGT GGAG 14

(2) INFORMATION FOR SEQUENCE ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

CTGTGGTTGA AGTG 14

(2) INFORMATION FOR SEQUENCE ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GTTGTAGGTG ACCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

CTGTGTTGTA GGTG 14

(2) INFORMATION FOR SEQUENCE ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GACTCAAACG TGTC 14

(2) INFORMATION FOR SEQUENCE ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

CATGGACTCA AACG 14

(2) INFORMATION FOR SEQUENCE ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

CGAATGTATA CCGG 14

(2) INFORMATION FOR SEQUENCE ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

CCGAATGTAT ACCG 14

(2) INFORMATION FOR SEQUENCE ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

GCCGAATGTA TACC 14

(2) INFORMATION FOR SEQUENCE ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

GTAGTTGTAG GGAC 14

(2) INFORMATION FOR SEQUENCE ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

TAGAAAGGTA GTTGTAGG 18

(2) INFORMATION FOR SEQUENCE ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

GTAGAAAGGT AGTTGTAG 18

(2) INFORMATION FOR SEQUENCE ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

CGTAGAAAGG TAGTTG 16

(2) INFORMATION FOR SEQUENCE ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

CCGTAGAAAG GTAG 14

(2) INFORMATION FOR SEQUENCE ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

GACCATAGCA CACT 14

(2) INFORMATION FOR SEQUENCE ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GGATATTGGC ACTG 14

(2) INFORMATION FOR SEQUENCE ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

CCTGGATATT GGCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

GCTCCCAAAG ATCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

CCCATCAAAG CTCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

CAAACACTTG GAGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

GTCTCAAACA CTTGGA 16

(2) INFORMATION FOR SEQUENCE ID NO: 41

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

GAGTCTCAAA CACTTG 16

(2) INFORMATION FOR SEQUENCE ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

GTAACCTGTG ATCTCT 16

(2) INFORMATION FOR SEQUENCE ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

GGTAACCTGT GATC 14

(2) INFORMATION FOR SEQUENCE ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

GTATAGGTAA CCTGTG 16

(2) INFORMATION FOR SEQUENCE ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

TGAGATGTAT AGGTAACC 18

(2) INFORMATION FOR SEQUENCE ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

TGCTGAGATG TATAGG 16

(2) INFORMATION FOR SEQUENCE ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

CCATGCTGAG ATGT 14

(2) INFORMATION FOR SEQUENCE ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

GGATTACTTG CAGG 14

(2) INFORMATION FOR SEQUENCE ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

TGTTATGGTG GATGAG 16

(2) INFORMATION FOR SEQUENCE ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

GGTGTTATGG TGGA 14

(2) INFORMATION FOR SEQUENCE ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

GCAGTTGACA CACT 14

(2) INFORMATION FOR SEQUENCE ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

AGTACTCGGC ATTC 14

(2) INFORMATION FOR SEQUENCE ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

CATTCACATA CTCCCT 16

(2) INFORMATION FOR SEQUENCE ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

TCCAAAACAG GTCACT 16

(2) INFORMATION FOR SEQUENCE ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

GGTCCTTATA GTGG 14

(2) INFORMATION FOR SEQUENCE ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

CAGAATGCCA ACCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

ACGAGAATGC CAAC 14

(2) INFORMATION FOR SEQUENCE ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

GATCCCAAAG ACCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

TCGCTTGATG AGGA 14

(2) INFORMATION FOR SEQUENCE ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

CATCGTGTAC TTCC 14

(2) INFORMATION FOR SEQUENCE ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

GCATCGTGTA CTTC 14

(2) INFORMATION FOR SEQUENCE ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

ACTGTGCCAA AAGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

CTTGTAGACT GTGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

CCCTTGTAGA CTGT 14

(2) INFORMATION FOR SEQUENCE ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

TCAACACTTT GATGGC 16

(2) INFORMATION FOR SEQUENCE ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

CCCTCAACAC TTTG 14

(2) INFORMATION FOR SEQUENCE ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

GTGTTTTCCC TCAACA 16

(2) INFORMATION FOR SEQUENCE ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

GTATGCTTCG TCTAAG 16

(2) INFORMATION FOR SEQUENCE ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

CGTATGCTTC GTCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

CCATCACGTA TGCT 14

(2) INFORMATION FOR SEQUENCE ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

GCATAAGCTG TGTC 14

(2) INFORMATION FOR SEQUENCE ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

CATGGTCTAA GAGG 14

(2) INFORMATION FOR SEQUENCE ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

CAATCTGCAT ACACCA 16

(2) INFORMATION FOR SEQUENCE ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

GGCAATCTGC ATAC 14

(2) INFORMATION FOR SEQUENCE ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

CTGTCTCGTC AATG 14

(2) INFORMATION FOR SEQUENCE ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

CATAACTCCA CACATC 16

(2) INFORMATION FOR SEQUENCE ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

AGTCACACCA TAACTC 16

(2) INFORMATION FOR SEQUENCE ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

ACAGTCACAC CATAAC 16

(2) INFORMATION FOR SEQUENCE ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

CCCCAAAAGT CATC 14

(2) INFORMATION FOR SEQUENCE ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

TCGTAAGGTT TGGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

GATCCCATCG TAAG 14

(2) INFORMATION FOR SEQUENCE ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

CAATGGTGCA GATG 14

(2) INFORMATION FOR SEQUENCE ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

GACATCAATG GTGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

GTAGACATCA ATGGTG 16

(2) INFORMATION FOR SEQUENCE ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

CATGATCATG TAGACATC 18

(2) INFORMATION FOR SEQUENCE ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

CCATGATCAT GTAGAC 16

(2) INFORMATION FOR SEQUENCE ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

CATTTGACCA TGATCATG 18

(2) INFORMATION FOR SEQUENCE ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

CCAACATTTG ACCATG 16

(2) INFORMATION FOR SEQUENCE ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

TCATCCAACA TTTGACCA 18

(2) INFORMATION FOR SEQUENCE ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

GAGTCAATCA TCCAACAT 18

(2) INFORMATION FOR SEQUENCE ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

CAGAGTCAAT CATCCA 16

(2) INFORMATION FOR SEQUENCE ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

CCGACATTCA GAGT 14

(2) INFORMATION FOR SEQUENCE ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

GAATTCAGAC ACCAAC 16

(2) INFORMATION FOR SEQUENCE ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

GATGACCACA AAGC 14

(2) INFORMATION FOR SEQUENCE ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

CCATCAAATA CATCGG 16

(2) INFORMATION FOR SEQUENCE ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

TCACCATCAA ATACATCG 18

(2) INFORMATION FOR SEQUENCE ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

CAACGTAGCC ATCA 14

(2) INFORMATION FOR SEQUENCE ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

ACGTCTTTGA CGAC 14

(2) INFORMATION FOR SEQUENCE ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

CAAAAACGTC TTTGACGA 18

(2) INFORMATION FOR SEQUENCE ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

GGCAAAAACG TCTTTG 16

(2) INFORMATION FOR SEQUENCE ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

CAAAGGCAAA AACGTC 16

(2) INFORMATION FOR SEQUENCE ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

GTGTCAAGTA CTCG 14

(2) INFORMATION FOR SEQUENCE ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

GTAATAGAGG TTGTCG 16

(2) INFORMATION FOR SEQUENCE ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

CCCAGTAATA GAGG 14

(2) INFORMATION FOR SEQUENCE ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

CATGGTGCTC ACTG 14

(2) INFORMATION FOR SEQUENCE ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

GTGCCTGTAC GTAC 14

Claims

1. An antisense nucleic acid or an effective derivative therefrom which is capable of treating or preventing neoplasms, immune diseases and/or diseases involving pathological angiogenesis, hybridizing with an area of the messenger RNA (mRNA) and/or DNA encoding c-erbB-2, comprising the following sequences identified in the listing under Seq. ID No. 1 - 105, having DNA- or RNA-type structure.

2. Antisense oligonucleotides of claim 1 wherein the oligonucleotides are modified oligonucleotides such as phosphorothioate derivatives.

3. Antisense nucleic acid or -oligonucleotides according to any one of the claims 1 and/or 2 obtainable by solid phase synthesis using phosphite triester chemistry by growing the nucleotide chain in 3'-5' direction in that the respective nucleotide is coupled to the first nucleotide which is covalently attached to the solid phase comprising the steps of

   - cleaving 5'DMT protecting group of the previous nucleotide,
   - adding the respective nucleotide for chain propagation,
   - modifying phosphite groups subsequently cap unreacted 5'-hydroxyl groups and
   - cleaving the oligonucleotide from the solid support,
   - followed by working up the synthesis product.

4. A pharmaceutical composition comprising an effective amount of a compound of any one of the claims 1 to 3 for the prevention and treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis.

5. Use of a compound according to any one of the claims 1 to 3 for the preparation of a pharmaceutical composition for the prevention and treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis.

6. Use of a compound according to any one of the claims 1 to 3 as diagnostic agent.

7. Method of treating or preventing neoplasms and/or immune diseases and diseases involving pathological angiogenesis by administering an effective amount of the compound according to any one of the claims 1 to 3 or a pharmaceutical composition of claim 4 to a patient suffering from disorders related with the expression of c-erbB-2.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/EP 94/04094

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 A61K31/70 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ERICKSON, R. & IZANT, J. 'Gene regulation: biology of antisense RNA and DNA'; 1992, RAVEN PRESS, Ltd., NEW YORK, USA pages 317-328, SCHLINGENSIEPEN, K.-H- & BRYSCH, W.: 'Phosphorothioate oligomers: inhibitors of oncogene expression in tumor cells and tools for gene function analysis' see the whole document --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 1995	04 -04- 1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCIENCE, vol. 230, 6 December 1985 LANCASTER, PA US, pages 1132-1139, COUSSENS, L. ET AL. 'Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene' see figure 3	1,2,4-7
Y	WO,A,92 19732 (GENSET) 12 November 1992 see page 22, line 0 - page 23, line 1 see page 32, line 26 - page 33, line 9	3
O,A	PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 32, March 1991 page 433 BRYSCH, W. ET AL. 'Inhibiting c-erbB-2 overexpression in human mammary carcinoma cells with phosphorothioate oligodeoxynucleotides' see abstract	1-7
A	WO,A,93 09788 (BAYLOR COLLEGE OF MEDICINE) 27 May 1993 see page 2, line 19 - page 3, line 10 see page 7, line 3 - line 16 see claims	1,4-7
A	WO,A,92 13063 (ONCOGENE SCIENCE, INC.) 6 August 1992 see page 5, line 21 - line 35 see page 15, line 23 - page 16, line 6 see page 31, line 18 - page 32, line 15 see page 49, line 14 - page 50, line 12 see claims 2,15-20,66,111-115 see claims 127-133	1,4-7

1

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/EP 94/04094

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In. .mation on patent family members

Internati Application No
PCT/EP 94/04094

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9219732	12-11-92	FR-A-	2675803	30-10-92
		AU-A-	1759692	21-12-92
		CA-A-	2102229	26-10-92
		EP-A-	0581848	09-02-94
		JP-T-	6506834	04-08-94
WO-A-9309788	27-05-93	NONE		
WO-A-9213063	06-08-92	AU-A-	1469292	27-08-92